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5 <110> Janssen Pharmaceutica N.V.

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<150> PCT/ EP03/10263

15 <151> 2003-09-12

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Gly Ser Tyr Lys Lys Ile Gly Tyr Tyr Asp Ser Thr Lys Asp Asp Leu	
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Ser Trp Ser Lys Thr Asp Lys Trp Ile Gly Gly Ser Pro Pro Ala Asp	
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Asp His Arg Ala Val Gly Met Ala Ile Tyr Asn Val Ala Val Leu Cys	
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Asn Asn Asn Glu Glu Glu Lys Ser Arg Leu Leu Glu Lys Glu Asn Arg	
885 890 895	
gaa ctg gaa aag atc att gct gag aaa gag gag cgt gtc tct gaa ctg	2736
Glu Leu Glu Lys Ile Ile Ala Glu Lys Glu Glu Arg Val Ser Glu Leu	
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cgc cat caa ctc cag tct cgg cag cag ctc cgc tcc cgg cgc cac cca	2784
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Lys	

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Ile His Pro Pro Trp Glu Gly Gly Ile Arg Tyr Arg Gly Leu Thr Arg
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Asp Gln Val Lys Ala Ile Asn Phe Leu Pro Val Asp Tyr Glu Ile Glu
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Tyr Val Cys Arg Gly Glu Arg Glu Val Val Gly Pro Lys Val Arg Lys
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Cys Leu Ala Asn Gly Ser Trp Thr Asp Met Asp Thr Pro Ser Arg Cys
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Val Arg Ile Cys Ser Lys Ser Tyr Leu Thr Leu Glu Asn Gly Lys Val
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Phe Leu Thr Gly Gly Asp Leu Pro Ala Leu Asp Gly Ala Arg Val Asp
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Phe Arg Cys Asp Pro Asp Phe His Leu Val Gly Ser Ser Arg Ser Ile
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Cys Ser Gln Gly Gln Trp Ser Thr Pro Lys Pro His Cys Gln Val Asn
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Arg Thr Pro His Ser Glu Arg Arg Ala Val Tyr Ile Gly Ala Leu Phe
165 170 175

Pro Met Ser Gly Gly Trp Pro Gly Gly Gln Ala Cys Gln Pro Ala Val
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Glu Met Ala Leu Glu Asp Val Asn Ser Arg Arg Asp Ile Leu Pro Asp
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Tyr Glu Leu Lys Leu Ile His His Asp Ser Lys Cys Asp Pro Gly Gln
210 215 220

Ala Thr Lys Tyr Leu Tyr Glu Leu Leu Tyr Asn Asp Pro Ile Lys Ile
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Ile Leu Met Pro Gly Cys Ser Ser Val Ser Thr Leu Val Ala Glu Ala
245 250 255

Ala Arg Met Trp Asn Leu Ile Val Leu Ser Tyr Gly Ser Ser Ser Pro
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Ala Leu Ser Asn Arg Gln Arg Phe Pro Thr Phe Phe Arg Thr His Pro
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Ser Ala Thr Leu His Asn Pro Thr Arg Val Lys Leu Phe Glu Lys Trp
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Gly Trp Lys Lys Ile Ala Thr Ile Gln Gln Thr Thr Glu Val Phe Thr
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Ser Thr Leu Asp Asp Leu Glu Glu Arg Val Lys Glu Ala Gly Ile Glu
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Ile Thr Phe Arg Gln Ser Phe Phe Ser Asp Pro Ala Val Pro Val Lys
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Asn Leu Lys Arg Gln Asp Ala Arg Ile Ile Val Gly Leu Phe Tyr Glu
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Thr Glu Ala Arg Lys Val Phe Cys Glu Val Tyr Lys Glu Arg Leu Phe
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Phe Lys Ile Tyr Asp Pro Ser Ile Asn Cys Thr Val Asp Glu Met Thr
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Glu Ala Val Glu Gly His Ile Thr Thr Glu Ile Val Met Leu Asn Pro
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Ala Asn Thr Arg Ser Ile Ser Asn Met Thr Ser Gln Glu Phe Val Glu
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Lys Leu Thr Lys Arg Leu Lys Arg His Pro Glu Glu Thr Gly Gly Phe
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Gln Glu Ala Pro Leu Ala Tyr Asp Ala Ile Trp Ala Leu Ala Leu Ala
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Leu Asn Lys Thr Ser Gly Gly Gly Gly Arg Ser Gly Val Arg Leu Glu
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Asp Phe Asn Tyr Asn Asn Gln Thr Ile Thr Asp Gln Ile Tyr Arg Ala
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Met Asn Ser Ser Ser Phe Glu Gly Val Ser Gly His Val Val Phe Asp
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Gly Ser Tyr Lys Lys Ile Gly Tyr Tyr Asp Ser Thr Lys Asp Asp Leu
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Ser Trp Ser Lys Thr Asp Lys Trp Ile Gly Gly Ser Pro Pro Ala Asp
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Gln Thr Leu Val Ile Lys Thr Phe Arg Phe Leu Ser Gln Lys Leu Phe
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Ile Ser Val Ser Val Leu Ser Ser Leu Gly Ile Val Leu Ala Val Val
595 600 605

Cys Leu Ser Phe Asn Ile Tyr Asn Ser His Val Arg Tyr Ile Gln Asn
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Ser Gln Pro Asn Leu Asn Asn Leu Thr Ala Val Gly Cys Ser Leu Ala
625 630 635 640

Leu Ala Ala Val Phe Pro Leu Gly Leu Asp Gly Tyr His Ile Gly Arg
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Asn Gln Phe Pro Phe Val Cys Gln Ala Arg Leu Trp Leu Leu Gly Leu
660 665 670

Gly Phe Ser Leu Gly Tyr Gly Ser Met Phe Thr Lys Ile Trp Trp Val
675 680 685

His Thr Val Phe Thr Lys Lys Glu Glu Lys Lys Glu Trp Arg Lys Thr
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Leu Glu Pro Trp Lys Leu Tyr Ala Thr Val Gly Leu Leu Val Gly Met

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Thr Ile Glu Thr Phe Ala Lys Glu Glu Pro Lys Glu Asp Ile Asp Val						
	740		745		750	
Ser Ile Leu Pro Gln Leu Glu His Cys Ser Ser Arg Lys Met Asn Thr						
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Trp Leu Gly Ile Phe Tyr Gly Tyr Lys Gly Leu Leu Leu Leu Leu Gly						
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Asp His Arg Ala Val Gly Met Ala Ile Tyr Asn Val Ala Val Leu Cys						
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Leu Ile Thr Ala Pro Val Thr Met Ile Leu Ser Ser Gln Gln Asp Ala						
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Ala Phe Ala Phe Ala Ser Leu Ala Ile Val Phe Ser Ser Tyr Ile Thr						
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Leu Val Val Leu Phe Val Pro Lys Met Arg Arg Leu Ile Thr Arg Gly						
	850		855		860	
Glu Trp Gln Ser Glu Ala Gln Asp Thr Met Lys Thr Gly Ser Ser Thr						
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Asn Asn Asn Glu Glu Glu Lys Ser Arg Leu Leu Glu Lys Glu Asn Arg						
	885		890		895	
Glu Leu Glu Lys Ile Ile Ala Glu Lys Glu Glu Arg Val Ser Glu Leu						
	900		905		910	
Arg His Gln Leu Gln Ser Arg Gln Gln Leu Arg Ser Arg Arg His Pro						
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Pro Thr Pro Pro Glu Pro Ser Gly Gly Leu Pro Arg Gly Pro Pro Glu						
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Lys

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 Pro Pro Pro Pro Ala Arg Leu Leu Leu Leu Leu Leu Pro Leu Leu
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 ctg cct ctg gcg ccc ggg gcc tgg ggc tgg gcg cgg ggc gcc ccc cgg 144
 Leu Pro Leu Ala Pro Gly Ala Trp Gly Trp Ala Arg Gly Ala Pro Arg
 35 40 45
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 Pro Pro Pro Ser Ser Pro Pro Leu Ser Ile Met Gly Leu Met Pro Leu
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 Thr Lys Glu Val Ala Lys Gly Ser Ile Gly Arg Gly Val Leu Pro Ala
 65 70 75 80
 gtg gaa ctg gcc atc gag cag atc cgc aac gag tca ctc ctg cgc ccc 288
 Val Glu Leu Ala Ile Glu Gln Ile Arg Asn Glu Ser Leu Leu Arg Pro
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 tac ttc ctc gac ctg cgg ctc tat gac acg gag tgc gac aac gca aaa 336
 Tyr Phe Leu Asp Leu Arg Leu Tyr Asp Thr Glu Cys Asp Asn Ala Lys
 100 105 110
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 Gly Leu Lys Ala Phe Tyr Asp Ala Ile Lys Tyr Gly Pro Asn His Leu
 115 120 125
 atg gtg ttt gga ggc gtc tgt cca tcc gtc aca tcc atc att gca gag 432
 Met Val Phe Gly Gly Val Cys Pro Ser Val Thr Ser Ile Ile Ala Glu
 130 135 140

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cct gtt cta gcc gat aag aaa aaa tac cct tat ttc ttt cgg acc gtc Pro Val Leu Ala Asp Lys Lys Lys Tyr Pro Tyr Phe Phe Arg Thr Val 165 170 175	528
cca tca gac aat gcg gtg aat cca gcc att ctg aag ttg ctc aag cac Pro Ser Asp Asn Ala Val Asn Pro Ala Ile Leu Lys Leu Leu Lys His 180 185 190	576
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Ile Gln Asp Phe Asn Tyr Thr Asp His Thr Leu Gly Arg Ile Ile Leu	
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Phe Arg Asn Gly Glu Arg Met Gly Thr Ile Lys Phe Thr Gln Phe Gln	
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Asp Ser Arg Glu Val Lys Val Gly Glu Tyr Asn Ala Val Ala Asp Thr	
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Leu Glu Ile Ile Asn Asp Thr Ile Arg Phe Gln Gly Ser Glu Pro Pro	
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Lys Asp Lys Thr Ile Ile Leu Glu Gln Leu Arg Lys Ile Ser Leu Pro	
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Leu	Cys	Ile	Leu	Ile	Cys	Trp	Gln	Ala	Val	Asp	Pro	Leu	Arg	Arg	Thr	
	610					615					620					
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Val	Glu	Lys	Tyr	Ser	Met	Glu	Pro	Asp	Pro	Ala	Gly	Arg	Asp	Ile	Ser	
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Ile	Arg	Pro	Leu	Leu	Glu	His	Cys	Glu	Asn	Thr	His	Met	Thr	Ile	Trp	
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Cys	Leu	Val	Phe	Val	Pro	Lys	Leu	Ile	Thr	Leu	Arg	Thr	Asn	Pro	Asp	
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Ala	Ala	Thr	Gln	Asn	Arg	Arg	Phe	Gln	Phe	Thr	Gln	Asn	Gln	Lys	Lys	
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Glu	Asp	Ser	Lys	Thr	Ser	Thr	Ser	Val	Thr	Ser	Val	Asn	Gln	Ala	Ser	
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Thr	Ser	Arg	Leu	Glu	Gly	Leu	Gln	Ser	Glu	Asn	His	Arg	Leu	Arg	Met	
	785				790					795					800	
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Lys	Ile	Thr	Glu	Leu	Asp	Lys	Asp	Leu	Glu	Glu	Val	Thr	Met	Gln	Leu	
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Gln	Asp	Thr	Pro	Glu	Lys	Thr	Thr	Tyr	Ile	Lys	Gln	Asn	His	Tyr	Gln	

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Glu	Leu	Asn	Asp	Ile	Leu	Asn	Leu	Gly	Asn	Phe	Thr	Glu	Ser	Thr	Asp					
835					840					845										
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885					890					895										
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915					920					925										
cat	gtg	cca	ccc	tcc	ttc	cga	gtc	atg	gtc	tcg	ggc	ctg				2823				
His	Val	Pro	Pro	Ser	Phe	Arg	Val	Met	Val	Ser	Gly	Leu								
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<400> 4

Met	Ala	Ser	Pro	Arg	Ser	Ser	Gly	Gln	Pro	Gly	Pro	Pro	Pro	Pro	Pro
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Pro	Pro	Pro	Pro	Ala	Arg	Leu	Leu	Leu	Leu	Leu	Leu	Leu	Pro	Leu	Leu
20						25						30			

Leu	Pro	Leu	Ala	Pro	Gly	Ala	Trp	Gly	Trp	Ala	Arg	Gly	Ala	Pro	Arg
35					40					45					

Pro	Pro	Pro	Ser	Ser	Pro	Pro	Leu	Ser	Ile	Met	Gly	Leu	Met	Pro	Leu
50					55						60				

Thr	Lys	Glu	Val	Ala	Lys	Gly	Ser	Ile	Gly	Arg	Gly	Val	Leu	Pro	Ala
65				70					75				80		

Val Glu Leu Ala Ile Glu Gln Ile Arg Asn Glu Ser Leu Leu Arg Pro
85 90 95

Tyr Phe Leu Asp Leu Arg Leu Tyr Asp Thr Glu Cys Asp Asn Ala Lys
100 105 110

Gly Leu Lys Ala Phe Tyr Asp Ala Ile Lys Tyr Gly Pro Asn His Leu
115 120 125

Met Val Phe Gly Gly Val Cys Pro Ser Val Thr Ser Ile Ile Ala Glu
130 135 140

Ser Leu Gln Gly Trp Asn Leu Val Gln Leu Ser Phe Ala Ala Thr Thr
145 150 155 160

Pro Val Leu Ala Asp Lys Lys Lys Tyr Pro Tyr Phe Phe Arg Thr Val
165 170 175

Pro Ser Asp Asn Ala Val Asn Pro Ala Ile Leu Lys Leu Leu Lys His
180 185 190

Tyr Gln Trp Lys Arg Val Gly Thr Leu Thr Gln Asp Val Gln Arg Phe
195 200 205

Ser Glu Val Arg Asn Asp Leu Thr Gly Val Leu Tyr Gly Glu Asp Ile
210 215 220

Glu Ile Ser Asp Thr Glu Ser Phe Ser Asn Asp Pro Cys Thr Ser Val
225 230 235 240

Lys Lys Leu Lys Gly Asn Asp Val Arg Ile Ile Leu Gly Gln Phe Asp
245 250 255

Gln Asn Met Ala Ala Lys Val Phe Cys Cys Ala Tyr Glu Glu Asn Met
260 265 270

Tyr Gly Ser Lys Tyr Gln Trp Ile Ile Pro Gly Trp Tyr Glu Pro Ser
275 280 285

Trp Trp Glu Gln Val His Thr Glu Ala Asn Ser Ser Arg Cys Leu Arg
290 295 300

Lys Asn Leu Leu Ala Ala Met Glu Gly Tyr Ile Gly Val Asp Phe Glu
305 310 315 320

Pro Leu Ser Ser Lys Gln Ile Lys Thr Ile Ser Gly Lys Thr Pro Gln
325 330 335

Gln Tyr Glu Arg Glu Tyr Asn Asn Lys Arg Ser Gly Val Gly Pro Ser
340 345 350

Lys Phe His Gly Tyr Ala Tyr Asp Gly Ile Trp Val Ile Ala Lys Thr
355 360 365

Leu Gln Arg Ala Met Glu Thr Leu His Ala Ser Ser Arg His Gln Arg
370 375 380

Ile Gln Asp Phe Asn Tyr Thr Asp His Thr Leu Gly Arg Ile Ile Leu
385 390 395 400

Asn Ala Met Asn Glu Thr Asn Phe Phe Gly Val Thr Gly Gln Val Val
405 410 415

Phe Arg Asn Gly Glu Arg Met Gly Thr Ile Lys Phe Thr Gln Phe Gln
420 425 430

Asp Ser Arg Glu Val Lys Val Gly Glu Tyr Asn Ala Val Ala Asp Thr
435 440 445

Leu Glu Ile Ile Asn Asp Thr Ile Arg Phe Gln Gly Ser Glu Pro Pro
450 455 460

Lys Asp Lys Thr Ile Ile Leu Glu Gln Leu Arg Lys Ile Ser Leu Pro
465 470 475 480

Leu Tyr Ser Ile Leu Ser Ala Leu Thr Ile Leu Gly Met Ile Met Ala
485 490 495

Ser Ala Phe Leu Phe Phe Asn Ile Lys Asn Arg Asn Gln Lys Leu Ile
500 505 510

Lys Met Ser Ser Pro Tyr Met Asn Asn Leu Ile Ile Leu Gly Gly Met
515 520 525

Leu Ser Tyr Ala Ser Ile Phe Leu Phe Gly Leu Asp Gly Ser Phe Val

530

535

540

Ser Glu Lys Thr Phe Glu Thr Leu Cys Thr Val Arg Thr Trp Ile Leu
 545 550 555 560

Thr Val Gly Tyr Thr Thr Ala Phe Gly Ala Met Phe Ala Lys Thr Trp
 565 570 575

Arg Val His Ala Ile Phe Lys Asn Val Lys Met Lys Lys Lys Ile Ile
 580 585 590

Lys Asp Gln Lys Leu Leu Val Ile Val Gly Gly Met Leu Leu Ile Asp
 595 600 605

Leu Cys Ile Leu Ile Cys Trp Gln Ala Val Asp Pro Leu Arg Arg Thr
 610 615 620

Val Glu Lys Tyr Ser Met Glu Pro Asp Pro Ala Gly Arg Asp Ile Ser
 625 630 635 640

Ile Arg Pro Leu Leu Glu His Cys Glu Asn Thr His Met Thr Ile Trp
 645 650 655

Leu Gly Ile Val Tyr Ala Tyr Lys Gly Leu Leu Met Leu Phe Gly Cys
 660 665 670

Phe Leu Ala Trp Glu Thr Arg Asn Val Ser Ile Pro Ala Leu Asn Asp
 675 680 685

Ser Lys Tyr Ile Gly Met Ser Val Tyr Asn Val Gly Ile Met Cys Ile
 690 695 700

Ile Gly Ala Ala Val Ser Phe Leu Thr Arg Asp Gln Pro Asn Val Gln
 705 710 715 720

Phe Cys Ile Val Ala Leu Val Ile Ile Phe Cys Ser Thr Ile Thr Leu
 725 730 735

Cys Leu Val Phe Val Pro Lys Leu Ile Thr Leu Arg Thr Asn Pro Asp
 740 745 750

Ala Ala Thr Gln Asn Arg Arg Phe Gln Phe Thr Gln Asn Gln Lys Lys
 755 760 765

Glu Asp Ser Lys Thr Ser Thr Ser Val Thr Ser Val Asn Gln Ala Ser
770 775 780

Thr Ser Arg Leu Glu Gly Leu Gln Ser Glu Asn His Arg Leu Arg Met
785 790 795 800

Lys Ile Thr Glu Leu Asp Lys Asp Leu Glu Glu Val Thr Met Gln Leu
805 810 815

Gln Asp Thr Pro Glu Lys Thr Thr Tyr Ile Lys Gln Asn His Tyr Gln
820 825 830

Glu Leu Asn Asp Ile Leu Asn Leu Gly Asn Phe Thr Glu Ser Thr Asp
835 840 845

Gly Gly Lys Ala Ile Leu Lys Asn His Leu Asp Gln Asn Pro Gln Leu
850 855 860

Gln Trp Asn Thr Thr Glu Pro Ser Arg Thr Cys Lys Asp Pro Ile Glu
865 870 875 880

Asp Ile Asn Ser Pro Glu His Ile Gln Arg Arg Leu Ser Leu Gln Leu
885 890 895

Pro Ile Leu His His Ala Tyr Leu Pro Ser Ile Gly Gly Val Asp Ala
900 905 910

Ser Cys Val Ser Pro Cys Val Ser Pro Thr Ala Ser Pro Arg His Arg
915 920 925

His Val Pro Pro Ser Phe Arg Val Met Val Ser Gly Leu
930 935 940